--In contrast, the effector caspases such as caspase-3, -6 and -7 have shorter pro-domains and are not recruited by the death receptors. As a result, these caspases remain dormant until activated directly by the initiator caspases via proteolytic cleavage (Fernandez-Alnemri *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:7464-7469; Srinivasa *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14486-14491). Once activated, the effector caspases rapidly dismantle important structural and regulatory components of the cell, leading to the characteristic apoptotic phenotype observed in cells undergoing apoptosis (Nicholson and Thornberry, 1997, *Trends Biochem. Sci.* 257:299-306).--

Please insert at page 58, line 15, the Sequence Listing attached hereto.

REMARKS

Applicant has hereinabove amended the specification to correct typographical errors in the citations of two references referred to in the specification. Further, Applicant has submitted herewith a copy of the original specification pages in which changes were made with the changes shown in red ink. Applicant respectfully submits that no new matter has been added.

Applicant has also amended the specification to include a Sequence Listing. As noted above, Applicants have attached a paper copy of the Sequence Listing and in addition, Applicants have enclosed a computer readable copy of the Sequence Listing. Applicant respectfully submits that the content of the Sequence Listing recorded in computer readable form is identical to the content of the paper copy of the Sequence Listing. Further, Applicant respectfully submits that no new matter has been added in the Sequence Listing.

In view of the foregoing, it is respectfully submitted that this application is now in condition for allowance and favorable reconsideration and prompt notice of allowance are earnestly solicited.

Respectfully submitted,

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Enclosure: Copy of Original Specification Pages (with changes shown in red ink)
Computer Readable Copy and Paper Copy of Sequence Listing

Caspase-10 [10]		Initiator	17/12	unknown
Caspase-11 [11]		Cytokine processing	20/10	unknown
Caspase-12 [12]		Cytokine processing	20/10	unknown
Caspase-13 [13]		Cytokine processing	20/10	unknown
Caspase-14 [14]		Cytokine processing	20/10	unknown

Key to Table 1

[1] Thornberry *et al.* (1992) *Nature* **356**:766-774
[2] Li *et al.* (1997) *J. Biol. Chem.* **272**:21010-7
[3] Alnemri *et al.* (1996) *Cell* **87**:171
[4] Kamada *et al.* (1997) *Oncogene* **15**:285-90
[5] Kamada *et al.* (1997) *Cell Death and Differentiation* **4(6)**:473-478
[6] LeBlanc *et al.* (1999) *J. Biol. Chem.* **274**:23426-36
[7] Marcelli *et al.* (1998) *Cancer Res.* **58**:76-83
[8] Scaffidi *et al.* (1997) *J. Biol. Chem.* **272**:26953-8
[9] ~~Srinivasula *et al.* (1996) *J. Biol. Chem.* **271**:27099-106~~ Srinivasa et al. (1996) J. Biol. Chem. 273: 10107-10111
[10] Ng *et al.* (1999) *J. Biol. Chem.* **274**:10301-8
[11] Wang *et al.* (1998) *Cell* **92**:501-9
[12] Nakagawa *et al.* (2000) *Nature* **403**:98-103
[13] Humke *et al.* (1998) *J. Biol. Chem.* **273**:15702-7
[14] Hu *et al.* (1998) *J. Biol. Chem.* **273**:29648-53

Table 1 shows the properties of several known caspases.

All caspases share a common structure. The caspase pro-enzyme contains an N-terminal pro-domain, a large subunit containing the active site cysteine (within a conserved QACXG motif) and a small subunit which also contributes residues to the inter-subunit active site (Wilson, Black, Thomson *et. al.* (1994) *Nature* **370**, 270-274; Rotonda, Nicholson, Fazil *et al.* (1996) *Nat. Struct. Biol.* **3**, 619-25; Thornberry, Rano, Peterson *et al.* (1997) *J. Biol. Chem.* **272**, 17907-17911). Upon auto-activation or

activation by other caspases, the pro-domain is cleaved at an aspartate residue and an interdomain linker is cleaved at one or two aspartate residues, thereby converting the single-chain enzyme into a enzymatically-active heterodimer (comprising a large subunit and a small subunit). The heterodimer can subsequently dimerise into a tetramer.

Each caspase active site has a conserved positively charged 'S1 pocket', to bind the negatively charged aspartate 'P1' residue in the substrate peptide. Thus, all caspases cleave solely after aspartate residues. However, members of the caspase family exhibit different tetrameric peptide substrate specificities (see Table 1).

The upstream (or initiator) caspases, *e.g.* caspases-2, -8, -9 and-10, have a large pro-domain, which is thought to be involved in the recruitment of such caspases by 'death receptors' (see Cohen, 1997, *Biochem.* **326**:1-16; Kischkel et al., 1995, *EMBO J.* **14**:5579-5588). Association of the initiator receptors with the death complexes results in these enzymes being brought into close proximity with each other, which is thought to facilitate their activation by autocatalytic processing (Yang *et al.*, 1988, *Mol. Cell.* **1**:319-325; Muzio *et al.*, 1998, *J. Biol. Chem.* 273:2926-2930).

In contrast, the effector caspases such as caspase-3, -6 and –7 have shorter pro-domains and are not recruited by the death receptors. As a result, these caspases remain dormant until activated directly by the initiator caspases via proteolytic cleavage (Fernandez-Alnemri *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:7464-7469; ~~Srinivasula~~ Srinivasa et al., 1996, *Proc. Natl. Acad. Sci. USA* 93:~~13706-13711~~ 14486-14491). Once activated, the effector caspases rapidly dismantle important structural and regulatory components of the

cell, leading to the characteristic apoptotic phenotype observed in cells undergoing apoptosis (Nicholson and Thornberry, 1997, *Trends Biochem. Sci.* 257:299-306).

By "a constitutively active caspase" we include a protein or peptide which exhibits cysteine-bearing aspartate protease activity sufficient to induce apoptosis, *i.e.* a caspase in an activated form. Alternatively, the constitutively active caspase may comprise a precursor of such an active caspase that is able to *spontaneously* self-catalyse its conversion to the active caspase.

It will be appreciated that the cytotoxic portion comprising a constitutively active caspase or having substantially the same apoptosis-inducing activity as the said caspases may act at any point in the apoptotic cascade of events (as described above). For example, the cytotoxic portion may comprise a constitutively active variant of an effector caspase, such as caspase-3, caspase-6 or caspase-7, which directly triggers downstream apoptotic events. Alternatively, the cytotoxic portion may comprise a constitutively active variant of an initiator caspase such as caspase-2, caspase-8, caspase-9 or caspase-10 which acts upon the effector caspases to induce apoptosis.

In a preferred embodiment, the cytotoxic portion is a variant of a naturally-occurring caspase, said variant being constitutively active such that it is spontaneously active without the need for activation by other components of the apoptotic cascade.

Exemplary naturally occurring caspases are described in Table 1.